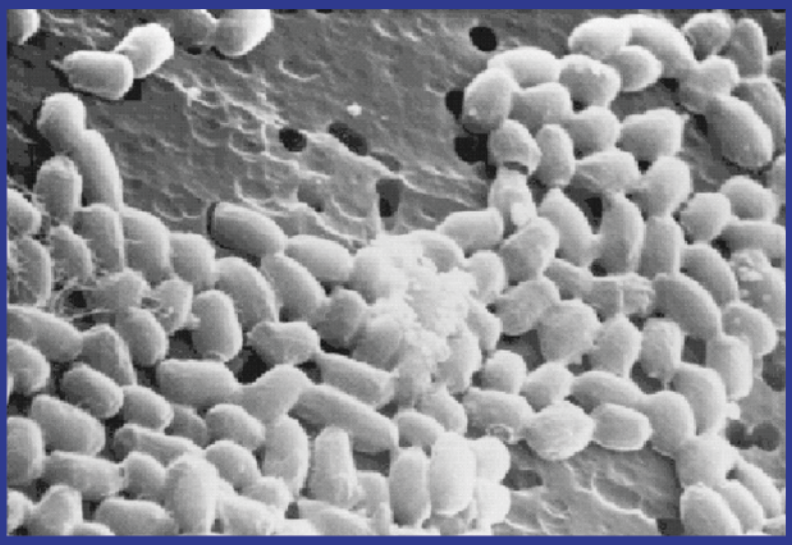
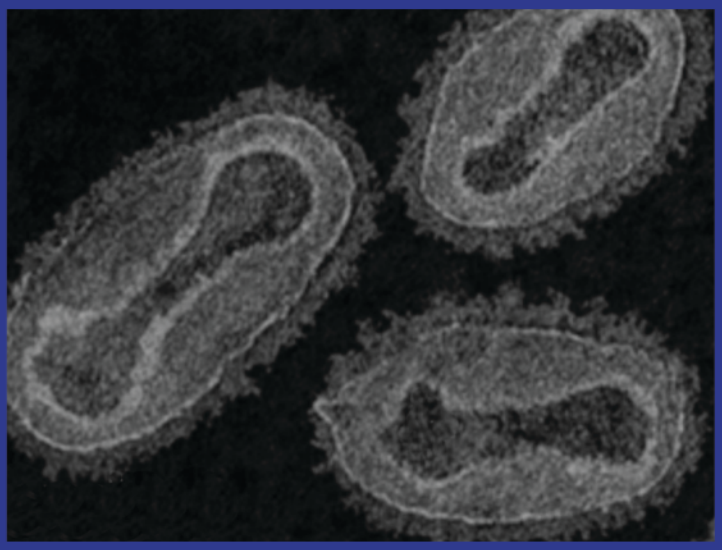
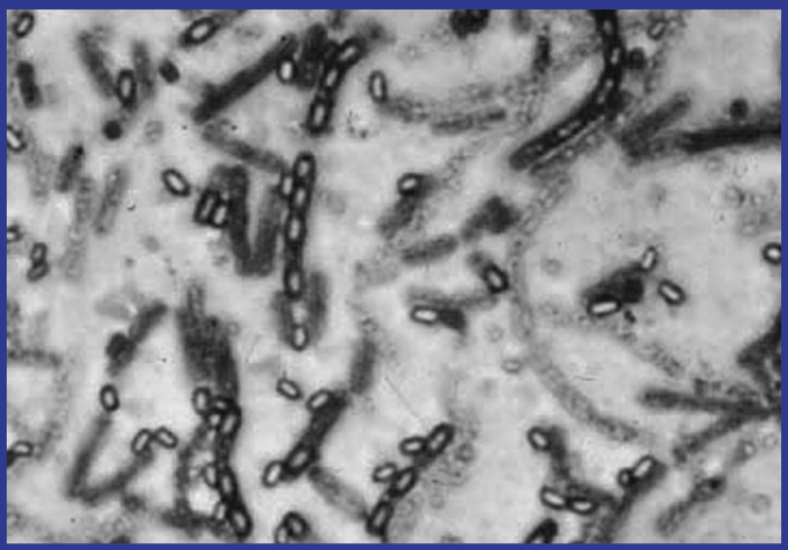
February 2002

NIAID Strategic Plan for Biodefense Research







Responding Through Research

National Institute of Allergy and Infectious Diseases
NATIONAL INSTITUTES OF HEALTH

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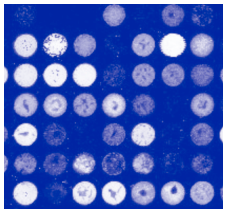
Responding



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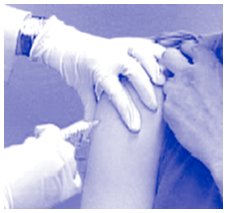

Research

National Institute of Allergy and Infectious Diseases
NATIONAL INSTITUTES OF HEALTH

NIAID Strategic Plan for Biodefense Research

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Introduction

Recent deliberate exposure of the civilian population of the United States to *Bacillus anthracis* spores by means of the United States Postal Service revealed a gap in the nation's overall preparedness against bioterrorism. These attacks uncovered an unmet need for tests to rapidly diagnose, vaccines and immunotherapies to prevent, and drugs and biologics to cure disease caused by agents of bioterrorism. An important component of the overall effort to fulfill these needs is biomedical research, and in this regard, we need a substantial and accelerated research and development agenda to accomplish short- and long-term goals aimed at protection of the United States and the world population against present and future attacks by these agents.

Definition of Bioterrorism

For the purposes of this plan and the research agenda that follows from it, bioterrorism is defined as the use of microorganisms that cause human disease, or of toxins derived from them, to harm people or to elicit widespread fear or intimidation of society for political or ideological goals. From a scientific and medical perspective, this form of terrorism is best seen as a variant of the general problem of emerging infectious diseases, the only difference being that increased virulence or spread into a susceptible population is a deliberate act of man rather than a consequence of natural evolution. The NIAID strategic plan focuses on this concept of bioterrorism. Closely related, but separate from it, are acts of terrorism resulting from the use of chemical toxins, nuclear energy, or organisms or toxins primarily affecting other animals or plants. Research on the public health consequences of these forms or terrorism are the purview of other U.S. Government agencies.

NIAID's Strategic Plan

NIAID is the primary Institute at the National Institutes of Health (NIH) for emerging infectious disease research, including that on agents of bioterrorism. The mission of NIAID is to carry out the research needed to understand the pathogenesis of these microbes and the host response to them, and to translate this knowledge into useful interventions and diagnostic tools for an effective response. Accordingly, NIAID is committed to an agenda of basic and translational research for bioterrorism defense, working with partners in academia, industry, and other private and public-sector agencies. NIAID has developed this Strategic Plan to guide the implementation of the necessary research and development program. It is important to emphasize that the Strategic Plan focuses on both basic research and the application of that basic research to predetermined goals, including the development of products such as diagnostics, therapeutics, and vaccines. In the traditional manner, NIAID will provide support for the pursuit of fundamental research questions concerning microbes and the specific and nonspecific host defense mechanisms against these microbes. In addition, the Institute will work with partners in the private and public sectors to ensure that the fruits of basic research are rapidly translated into products that can be used in the worldwide Biodefense and emerging infection effort. Finally, NIAID also will collaborate with other agencies and organizations on research related to other forms of terrorism where scientific overlap and mutual opportunity exist for scientific or public health gain.

Microbes and Their Products as Agents of Bioterrorism

A number of agents (select agents) are recognized as having bioterrorism potential (Lane et. al. *Nature Medicine*. 7, 1271-1273, 2001). Research focused on these select agents will be strongly emphasized in our initial activities. We recognize that these select agents have characteristics in common with other pathogens, especially those recognized as causing naturally occurring emerging or reemerging diseases. Biologic agents that have potential to become civilian bioterrorist agents, and will be emphasized in the plan, have many of the following characteristics:

- High morbidity and mortality
- Potential for person-to-person transmission, directly or by vector
- Low infective dose and high infectivity by aerosol, with a commensurate ability to cause large outbreaks
- Ability to contaminate food and water supplies
- Lack of a specific diagnostic test and/or effective treatment
- Lack of a safe and effective vaccine
- Potential to cause anxiety in the public and in health care workers
- Potential to be weaponized

The Strategic Plan should not be limited to preexisting lists of agents (CDC Category A, B, and C—www.bt.cdc.gov/Agent/Agentlist.asp#categoryadiseases) but should remain flexible and based on characteristics that make an agent a feasible threat against civilian populations. Agents that fit some or all of these criteria will be given high priority for research and development at NIAID (see NIAID http://www.niaid.nih.gov/dmid/bioterrorism/bandc_priority.htm).

This group includes pathogens or toxins that can contaminate food and water supplies and certain zoonotic agents that can spread infection to humans from domestic animals. A number of the emerging and reemerging pathogens, such as West Nile virus, influenza viruses, and drug-resistant *Streptococcus* and *Staphylococcus* also are recognized as having many characteristics that make them potential agents of bioterrorism. In addition, chimeric organisms engineered by relatively simple genetic manipulations may pose a significant threat. Goals include development of procedures to detect such agents and development of safe vaccines, biologics, and drugs to prevent or cure illness associated with them. For many reasons, particularly a lack of adequate facilities, study of these organisms has received little attention in the recent past. Therefore, the agenda must allow for acquisition of basic information on the pathogens and the host responses to them to allow development of effective Biodefense strategies.

Role of Host Defense in Combating Agents of Bioterrorism

In addition to research and development targeted to pathogens and their toxic products, we must study both the innate and adaptive host defense mechanisms to protect against infection and disease. We can exploit recent advances in understanding the innate immune system and host response to new generation vaccines to improve vaccines and to provide the means for enhancing immunity in threatened groups. This work may include development of specific immunotherapeutics and global advances in techniques of vaccinology, such as development of improved adjuvants to hasten onset of immunity and to increase the potency and lengthen the time of protective responses. Attention to duration of specific responses both at the B- and T-lymphocyte level is indicated to determine the immune status of persons under threat from agents of bioterrorism.

We must take special note of the populations within our communities that have compromised immunity or increased risk because of occupational exposure. In addition, the very young and the elderly, pregnant women, and those with immune function suppressed by disease or by drug regimens constitute groups with special vulnerability to the threat of infection. The research agenda must consider their needs.

Biocontainment Facilities Needed to Accomplish Research Goals

Achievement of the goals in this agenda requires the construction and certification of appropriate biocontainment facilities. Facilities and procedures for the handling of these potentially lethal agents in a manner aimed at eliminating the threat to laboratory and clinical personnel or to adjacent communities are an integral element of the program. These needs include facilities in which preclinical testing of vaccines and drugs can be accomplished using appropriate animal models, as well as clinical areas for isolation and study of patients exposed to bioterrorism agents.

Summary

The NIAID research and development plan comprises a broad and comprehensive agenda with the ultimate goal of providing a strong research base that translates

into effective products to combat agents of bioterrorism. The scientific needs and areas of NIAID research emphasis have been divided into six sections:

Biology of the Microbe	Therapeutics
Host Response	Diagnostics
Vaccines	Research Resources

As detailed below, the research agenda includes specific milestones directed at immediate goals as well as crucial enhancement of information and capability to deal with any present or future threats from biologic agents directed toward the civilian population.

Biology of the Microbe

Research into the basic biology and disease-causing mechanisms of pathogens that may be used as bioterrorist agents is critical to any efforts to develop interventions against bioterrorism. Such research includes identifying and understanding the microbial components that define a pathogen's life cycle, transmission, virulence, and invasiveness. Two recently developed, powerful, and increasingly important tools that can be used to dissect these factors are genomic sequencing and proteomics. These tools, which already have been applied to other complex organisms such as *H. plyori* and *M. tuberculosis*, have uncovered potential new targets for vaccines, therapeutics, and diagnostics.

Goals

- Expand the focus of genomic and proteomic data collection and analysis of microbes that can be used as bioterrorist agents by
  - Sequencing the genomes of select organisms and strains
  - Developing central bioinformatic resources or tools for rapid use of genomic information
  - Emphasizing research in genomic, proteomic, and structural analyses
- Expand basic research opportunities on microbial physiology, ecology, molecular pathogenesis, and animal model development for Category A, B, C, and D organisms

Host Response

To develop potent, safe, and effective vaccines, accurate diagnostics, and immunotherapeutics against microbes that can be used as bioterrorist agents, it is critical to improve our understanding of the complex parameters of innate and adaptive immunity. Because most potential bioterrorist agents would infect via the respiratory or oral routes, the plan includes specific studies on mucosal immunity at these sites. Crosscutting, multidisciplinary research will facilitate translation of the considerable body of basic knowledge that exists into vaccines, passive therapies, and diagnostic methods focused on bioterrorist agents. In the same way, new discoveries of immunologic principles or applications will help ensure a robust pipeline of improved or novel products.

Goals

- Expand the understanding of and ability to modify the innate and adaptive immune response to Category A, B, C, and D organisms by
  - Defining specialized innate and adaptive immune mechanisms used by the respiratory and/or oral-gastrointestinal systems
  - Mapping the protective epitopes for each agent, their respective toxins, and pathogenic factors using computational methods, genomics, proteomics, structural biology, and immunochemistry
  - Applying computational methods to model and predict immune responses
  - Refocusing basic immunology projects to include responses against potential bioterrorist agents
  - Expanding studies on host/pathogen interactions
- Facilitate clinical research on human immunology that will assist in identifying targets within innate and adaptive immune pathways by
  - Defining interactions between innate and adaptive immune systems
  - Discovering new recognition and signaling molecular pathways involved in innate immunity
  - Assessing relevant immune polymorphisms within the population

- Develop a comprehensive catalog of the variations in human immunologic responses

Vaccines

Vaccines are one of the most successful public health measures. The key features of vaccines to be developed for civilian use against bioterrorism agents will include the rapidity by which an immune response can be elicited, whether the vaccine can modulate the clinical course of an exposed person, the safety of the vaccine in all segments of the population, and the ease of administration or use. Because of the high public health concerns associated with these pathogens, smallpox and anthrax vaccine development will remain the highest priority.

Goals

Develop and test vaccine candidates for civilian bioterrorism threats with an immediate emphasis on the licensure of new generation smallpox and anthrax vaccines by

- Expanding the infrastructure for clinical testing and evaluation to rapidly test the new generation anthrax and smallpox vaccines under development
- Establishing a centralized immunology laboratory to develop and validate tests required for licensure of smallpox and anthrax vaccines
- Supporting the continued development of newer generation smallpox and anthrax vaccines with emphasis on increased safety and timely response
- Understanding and preventing complications of smallpox vaccine such as eczema vaccinatum and vaccinia gangrenosa
- Developing animal model capability and providing the required standardization and validation, including challenge of nonhuman primates, that will be necessary for licensure of smallpox and anthrax vaccines
- Identifying, prioritizing, and supporting the development of vaccines for other high-priority agents of potential bioterrorism
- Developing animal model capability and providing the required standardization and validation for development of vaccines against other select organisms

- Developing cell-culture-based approaches for viral vaccine development
- Developing improved vaccine approaches by focusing basic research interests to expand knowledge on
    - Potential targets for vaccine design
    - Vaccine delivery systems
    - B- and T-cell protective responses
    - Adjuvant development based on innate immunity
    - Potential regulation of the innate immune system as a primary defense
    - Differences in the innate and adaptive immune systems of human neonates, infants, pregnant women, immunocompromised populations, and the elderly (including genetic polymorphisms) that may influence responses to vaccines, both general and specific
- Ensuring manufacturing capacity for all delivery vehicles, vectors, and types of vaccines
- Expanding preclinical toxicology capability needed for vaccine development

Therapeutics

The development of new anti-infectives and immunotherapies, including antitoxins, and the screening of existing therapeutic agents to determine whether they have activity against select agents of bioterrorism remain a top priority. Although it has been shown that many of the bacterial agents in categories A, B, C, and D are sensitive to a number of antibiotics, licensure of these products for use in humans will require additional information. In addition, the underlying concern about the ease of development of antimicrobial resistance will factor into our need to increase this category of options. There are currently no antivirals or antisera licensed for use against smallpox and no antitoxin or other antisera licensed for use against anthrax. One antiviral, cidofovir, which is under IND for use as a backup to vaccinia immune globulin (VIG) in the setting of vaccinia immunizations and as a potential therapy in smallpox outbreaks, requires hospitalization during administration. VIG, which is required for the evaluation of smallpox vaccine candidates, is in extremely limited supply. The need to develop and license a

cadre of validated antimicrobials, alternatives to existing immunotherapies, and antitoxins, with a focus on smallpox and anthrax, will receive the highest priority.

Goals

Increase the number of licensed antimicrobials, immunotherapeutics, and antitoxins available for responding to select agents of bioterrorism through accelerated screening of new and existing agents by

- Expanding capacity for *in vitro* and *in vivo* evaluation of antimicrobials, immunotherapeutics, and antitoxins
- Developing a replacement to existing VIG
- Establishing additional agent-specific high-throughput screens
- Developing the animal model capability, including BSL-4 challenge on nonhuman primates and providing the required validation of animal models that will be necessary for licensure of new therapeutics for anthrax and smallpox
- Identifying, prioritizing, and supporting the development of other therapeutic interventions for specific agents
- Synthesizing, if needed, active lead compounds in sufficient quantities for preclinical pharmacokinetics, animal model efficacy, mechanisms of action, and toxicology studies
- Developing the animal model capability and the validation and standardization needed to assess efficacy
- Establishing required safety and pharmacokinetics data needed for licensure of new compounds
- Focusing basic research interests to expand knowledge on
    - Potential targets for therapeutic intervention
    - Discovery, characterization, optimization, and development of monoclonal and polyclonal antibodies

- Discovery and development of soluble receptors and mediators of the innate immune system as effective immunotherapeutic agents
- Differences in immune systems of human neonates, infants, pregnant women, immunocompromised subpopulations, and the elderly (including genetic polymorphisms), which may impact immunotherapeutics

Diagnostics

One of the hallmarks of a successful bioterrorist agent is clinical misdiagnosis or delayed diagnosis. The ability to rapidly identify the introduction of a bioterrorist agent into the civilian population will require highly sensitive, specific, inexpensive, and easy-to-use diagnostic tools located at primary care institutions. Ideally, these tests could also evaluate the possible spectrum of antimicrobial resistance and be connected to a central database. Centralized confirmatory testing also should be expanded to include routine evaluations of positive samples for weaponization, genetic profiling, and bioengineered properties. The theoretical ability to design and develop such assays exists. For example, we have microchip-based platforms, which could contain thousands of microbial signature profiles that are either nucleic acid or protein based. Identification of the microbial signatures is ongoing. If bioterrorism-based diagnostics could be combined with other more common and routine diagnostic needs, the value of these diagnostics to primary care institutions would ensure interest and use.

Goals

Expand interest and direction in the development of highly sensitive, specific, inexpensive, and easy-to-use tools for clinical diagnosis of potential agents of bioterrorism by

- Emphasizing this research interest
- Focusing genomic and proteomic analysis on identification of microbial signatures
- Providing standards for validation and comparison of potential products

Research Resources

The lack of routine clinical importance, and thus the absence of scientific and clinical expertise associated with the microbes, is another hallmark of a successful bioterrorist agent. The ability to develop the tools and interventions needed in a public health emergency will require the attention of the scientific community to these areas. The development of centralized sources of generalized as well as specific expertise in bioterrorism areas, such as *in vivo* and animal model development, production of standardized and validated reagents and tests, expertise in the development and humanization of antibodies, bioinformatics, diagnostic validation, and vaccine production (GLP/GMP pilot lots), will be required to speed the development of new generation products.

Goals

Expand the development of general and specific research resources to assist in the rapid development of new tools and interventions for use in bioterrorism by

- Developing 6 to12 regional Centers of Excellence for Bioterrorism and Emerging Diseases Research
- In addition to general capabilities, each center would develop a specialized expertise of importance to product development. Suggested areas of applied research emphasis include diagnostic development and validation, small- and large-animal model development, assay development and validation, immunotherapeutics, and host/pathogen interactions
- Encouraging and developing relationships between academia and industry
- Developing a centralized research reagent repository for standardized reagents that could be centrally controlled and accessed by appropriate investigators
- Developing BSL-3/4 capability at Centers of Excellence for Bioterrorism and Emerging Diseases Research
- Providing sufficient nonhuman primates to complete the testing and analysis of the therapeutic and vaccine products that are developed
- Expanding research training opportunities
- Expanding NIH clinical and basic research capabilities

Implications of Biodefense Research for Other Diseases

The positive spinoffs for other diseases that will result from the large investment in research on Biodefense will be substantial. First, many of the organisms in question and a host of other emerging infectious diseases and drug-resistant microbes are significant public health threats in endemic areas, especially in the developing world. Basic and translational research aimed at them will have direct and obvious benefit to the people threatened by them in nature. Second, research on microbial biology and pathogenesis of these organisms will enhance understanding of other more common and naturally occurring infectious diseases, both in the United States and around the world. Third, advancements in the arena of diagnostics, therapeutics, and vaccines will improve our ability to diagnose, treat, and prevent major killer-diseases, such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and reemerging diseases. Fourth, basic research will greatly enhance our understanding of the molecular and cellular mechanisms of the innate immune system and its relationship to the adaptive immune system, and lead to improvements in the treatment and prevention of immune-mediated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases. Finally, improved understanding of the mechanisms of regulation of the human immune system will have positive spinoffs for diseases such as cancer, immune-mediated neurologic diseases, and allergic and hypersensitivity diseases, as well as for the prevention of rejection of organ transplantation.

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